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Original article

Clostridioides difficile infection-associated cause-specific and all-cause mortality: a population-based cohort study

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ABSTRACT

Objectives: Clostridioides difficile infection (CDI) is a common healthcare-associated infection and leading cause of gastroenteritis-related mortality worldwide. However, data on CDI-associated mortality are scarce. We aimed to examine the association between CDI and all-cause and cause-specific mortality. We additionally explored contributing causes of mortality, including recurrent CDI, hospital- or community-acquired CDI, chronic comorbidities, and age.

Methods: This nationwide population-based cohort study (from 2006 to 2019) compared individuals with CDI with the entire Swedish background population using standardized mortality ratios. In addition, a matched-cohort design (1:10), utilizing multivariable Poisson-regression models, provided incidence rate ratios (IRRs) with 95% CIs.

Results: This study included 43 150 individuals with CDI and 355 172 controls. In total, 69.7% were ≥65 years, and 54.9% were female. CDI was associated with a 3- to 7-fold increased mortality rate (IRR = 3.5, 95% CI: 3.3–3.6; standardized mortality ratio = 6.8, 95% CI: 6.7–6.9) compared with the matched controls and Swedish background population, respectively. Mortality rates were highest for hospital-acquired CDI (IRR = 2.4, 95% CI: 1.9–3.2) and during the first CDI episode (IRR = 0.2, 95% CI: 0.2–0.3 for recurrent versus first CDI). Individuals with CDI had more chronic comorbidities than controls, yet mortality remained higher among CDI cases even after adjustment and stratification for comorbidity; CDI was associated with increased mortality (IRR = 6.1, 95% CI: 5.5–6.8), particularly among those without any chronic comorbidities.

Discussion: CDI was associated with elevated all-cause and cause-specific mortality, despite possible confounding by ill health. Mortality rates were consistently increased across sexes, all age groups, and comorbidity groups. **Annelies Boven, Clin Microbiol Infect 2023;29:1424**

Introduction

Clostridioides difficile is among the most common causes of healthcare-associated infections [1,2] and the leading cause of gastroenteritis-related mortality in the Western/industrialized world [3,4]. In the United States in 2015, it caused approximately 15% of all healthcare-associated infections [5]. The global annual incidence was recently estimated around 49 cases of *C. difficile* infections (CDI) per 100 000 individuals [6].

Risk factors for CDI incidence and mortality include exposures to antibiotics, proton pump inhibitors (PPIs), H_2-receptor antagonists, and non-steroidal anti-inflammatory drugs (NSAIDs) [7–11]. The CDI risk appears to increase by the number of previous CDI episodes (recurrences), older age, healthcare exposure, contact with other people with CDI, and comorbidities including inflammatory bowel

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disease, renal failure, haematologic cancer, diabetes mellitus, and immunosuppression [7,12,13].

CDI itself is associated with high morbidity and mortality: in multiple cohort and case-control studies on mostly elderly patients (mean/median age between 60 and 80 years) in the United States, Canada, England, Scotland, and the Netherlands, 30-day mortality ranged between 8% and 19% [10,14–19] and 1-year mortality between 11% and 37% [14,15,17]. In other regions, mortality figures and causes of death are largely under-reported. Even in countries with higher incidence, extensive population-based, nationwide data on cause-specific mortality are lacking.

This Swedish nationwide study, therefore, aimed to examine mortality after CDI diagnosis, assessing patient characteristics including chronic comorbidities, hospital or community acquisition, recurrence, causes of death, and duration of survival.

Methods

This Swedish population-based cohort study included all individuals with CDI episodes recorded between 1 January 2006 and 31 December 2019 (maximal 14-year follow-up), individually matched to up to ten controls (for more detail, see Supplementary methods). The study has been approved by the Swedish Ethical Review Authority (2020-02454), and reported according to STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines.

Exposure was defined as having a record of ≥1 CDI episode (anytime during the study period) and divided by community- and hospital-acquired CDI (hospital-acquired defined as a CDI episode during hospitalization). Recurrence was defined as a CDI episode within 8 weeks from the initial CDI diagnosis [20].

All-cause and cause-specific mortality (i.e. cardiovascular, cancer, respiratory, infectious, and sepsis) were selected based on the prevalence of the causes of death in Sweden (Table S1) [21].

Potential confounders and effect modifiers were chosen based on clinical knowledge, including age, sex, year of diagnosis, comorbidities, and the following prescription drug use: antibiotics, aspirin, H_2-receptor antagonists, PPIs, and NSAIDs (Tables S1 and S2) [7–9,12,13].

The association between CDI and mortality was investigated by applying two complementary methods, enhancing the robustness of the results. First, standardized mortality ratios (SMRs) were computed, comparing the observed mortality among the cases with the expected mortality based on the entire Swedish background population, stratified by sex, age, and calendar period. SMRs were computed for all-cause, cardiovascular- and cancer-specific mortality. Second, a matched-cohort design was utilized, providing 30-day, 180-day, and 1-year mortality ratios for all-cause and cause-specific mortality using (adjusted) IRRs computed by Poisson-regression modelling.

Results

Participants

This study included 43 150 individuals with CDI, of which 7251 (16.8%) had recurrent and 39 526 (91.6%) hospital-acquired CDI, and 355 172 controls (Fig. S1). Individuals with CDI had a median follow-up time of 2.0 years and controls of 5.5 years. Most individuals with CDI in this cohort were elderly: 74.8% were ≥65 years old, 21.3% were 20–64, and 3.9% were <20 years. A history of CDI was found among 1.2% of the individuals with CDI. CDI was associated with higher comorbidity scores than controls (mean 3.2 and 1.6, respectively). The most prominent differences were observed for individuals without any of the included comorbidities (14.2% cases and 40.6% controls), and those with the highest score, i.e. ≥5 (26.7% cases and 8.4% controls). Individuals with CDI received more prescriptions (from July 2005 onwards) than controls, especially PPIs (71.5% and 45.7%, respectively) and antibiotics (97.1% and 85.8%, respectively) (Table 1).

Individuals with recurrent CDI (rCDI) and non-rCDI had a similar follow-up. Individuals with rCDI included slightly more women and elderly. Furthermore, individuals with rCDI had higher comorbidity scores than those without recurrence, the largest differences found for scores 0 (13.1% versus 14.4%, respectively) and ≥5 (29.0% versus 26.2%, respectively). The average Charlson Comorbidity Index (CCI) score was 3.4 and 3.2, respectively. They received a similar number of prescriptions to individuals with non-rCDI.

Individuals with hospital-acquired CDI had a shorter follow-up than those with community-acquired CDI (1.7 versus 5.9 years), included more men and 2.29 times more elderly, and were on average 23 years older. Moreover, individuals with hospital-acquired CDI had significantly higher CCI scores: fewer individuals with score 0 (11.5% versus 47.5%) and more with ≥5 (28.2% versus 7.5%). The average CCI score was 3.4 and 1.4, respectively. They received more PPI (72.3% versus 60.1%) and aspirin (53.3% versus 24.8%) prescriptions than individuals with community-acquired CDI.

Absolute deaths

Overall, 61.6% of the CDI group died during the study period, compared with 28.8% of the controls (Table S3), with a large drop in survival early after infection as presented in the Kaplan-Meier curve (Fig. 1(a) and (b)). Most deaths in this study occurred among individuals aged ≥65 (89.6% CDI and 96.8% controls). Nevertheless, more individuals with CDI died among all age and comorbidity groups than controls of the same age (Table S4). The most common causes of deaths in this cohort were cardiovascular disease and cancer (56% cases and 60% controls) (Fig. 2).

Short-term and long-term risk

In this matched cohort, 9.2% of the CDI group versus 0.4% of the controls died within 30 days (Table S3). Overall, 26.4% versus 2.1% died within 180 days; and 33.1% versus 4.1% died within 1 year (Table S3). The largest mortality rates comparing individuals with CDI with individuals without CDI were found within the first year (Fig. 1(a)). Individuals with recurrent and non-rCDI presented with similar mortality rates (Fig. 1(b)).

CDI-associated mortality risk

CDI was associated with a 7-fold increase in all-cause mortality rate compared with the Swedish background population (SMR = 6.8, 95% CI: 6.7–6.9) (Table 2), and a 4-fold increase compared with the individually matched controls (IRR = 3.5, 95% CI: 3.3–3.6) (Table 3). The highest mortality rates were observed for cardiovascular- (SMR = 11.3, 95% CI: 11.1–11.5) and cancer-specific mortality (SMR = 8.8, 95% CI: 8.6–9.0) (Table 2).

Age and sex

Among individuals with CDI, 25.3% ($N = 2748$) of the <65-year-old group and 73.9% ($N = 23\,849$) of the ≥65-year-old group died, compared with, respectively, 3.1% ($N = 3291$) and 40.0% ($N = 99\,064$) among the controls during the 14-year study period. Compared with the Swedish background population, all-cause mortality rates in our study period decreased with age: individuals <65 years old had higher rates (all-cause SMR = 27.4, 95% CI: 26.2–28.5), than those ≥65 years (all-cause SMR = 6.3, 95% CI:

Table 1
Characteristics of Swedish individuals with CDI, including recurrent CDI (rCDI), non-recurrent CDI (non-rCDI), and community- and hospital-acquired CDI, and matched individuals without CDI (2006–2019)

Characteristics	Cases (n = 43 150)						Controls (n = 355 172)
	Total	rCDI (n = 7251)	Non-rCDI (n = 35 897)	Community-acquired (n = 3094)	Hospital-acquired (n = 39 526)	Unknown (n = 530)	
Follow-up time (y)							
Median (IQR)	1.95 (0.34–5.34)	2.10 (0.52–5.07)	1.92 (0.31–5.41)	5.87 (2.61–9.35)	1.72 (0.30–4.87)	3.51 (1.23–6.88)	5.48 (2.59–8.84)
Year of birth							
Median (IQR)	1936 (1927–1948)	1937 (1928–1948)	1936 (1927–1948)	1958 (1944–1984)	1935 (1927–1946)	1946 (1937–1962)	1939 (1930–1952)
Sex							
Male	19 780 (45.84%)	3145 (43.37%)	16 634 (46.34%)	1209 (39.08%)	18 335 (46.39%)	236 (44.53%)	159 897 (45.02%)
Female	23 370 (54.16%)	4106 (56.63%)	19 263 (53.66%)	1885 (60.92%)	21 191 (53.61%)	294 (55.47%)	195 275 (54.98%)
Age at CDI diagnosis[a]							
Mean (SD)	70.43 (±20.31)	70.79 (±19.83)	70.36 (±20.40)	48.38 (±25.80)	72.29 (±18.68)	61.03 (±21.87)	67.38 (±20.69)
Median (IQR)	76 (64–84)	76 (65–84)	76 (64–84)	54 (29–69)	77 (66–85)	68 (51–77)	73 (61–82)
0–19	1673 (3.88%)	292 (4.03%)	1381 (3.85%)	512 (16.55%)	1127 (2.85%)	34 (6.42%)	16 910 (4.76%)
20–64	9211 (21.35%)	1409 (19.43%)	7800 (21.73%)	1527 (49.35%)	7498 (18.97%)	186 (35.09%)	92 727 (26.11%)
≥65	32 266 (74.78%)	5550 (76.54%)	26 716 (74.42%)	1055 (34.10%)	30 901 (78.18%)	310 (58.49%)	245 535 (69.13%)
Year of CDI diagnosis[a]							
2006–2009	12 181 (28.23%)	1779 (24.53%)	10 402 (28.98%)	820 (26.50%)	11 231 (28.41%)	130 (24.53%)	112 024 (31.54%)
2010–2013	13 212 (30.62%)	1972 (27.20%)	11 239 (31.31%)	929 (30.03%)	12 154 (30.75%)	129 (244.34%)	107 248 (30.20%)
2014–2016	9201 (21.32%)	1773 (24.45%)	7428 (20.69%)	685 (22.14%)	8391 (21.23%)	125 (23.58%)	71 143 (20.03%)
2017–2019	8556 (19.83%)	1727 (23.82%)	6828 (19.02%)	660 (21.33%)	7750 (19.61%)	146 (27.55%)	64 757 (18.23%)
History of CDI[b]							
Yes	502 (1.16%)	140 (1.93%)	362 (1.01%)	42 (1.36%)	441 (1.12%)	19 (3.58%)	0 (0.00%)
No	42 648 (98.84%)	7111 (98.07%)	35 535 (98.99%)	3052 (98.64%)	39 085 (98.88%)	511 (96.42%)	355 172 (100.00%)
Charlson Comorbidity score							
Mean (SD)	3.21 (±2.47)	3.36 (±2.51)	3.18 (±2.47)	1.38 (±1.88)	3.36 (±2.46)	2.73 (±2.42)	1.61 (±1.88)
Median (IQR)	3 (1–5)	3 (2-5)	3 (1–5)	1 (0–2)	3 (2–5)	2 (1–4)	1 (0–3)
0	6126 (14.20%)	948 (13.07%)	5178 (14.42%)	1469 (47.48%)	4539 (11.48%)	118 (22.26%)	144 252 (40.61%)
1	5321 (12.33%)	834 (11.50%)	4487 (12.50%)	564 (18.23%)	4687 (11.86%)	70 (13.21%)	55 981 (15.76%)
2	8090 (18.75%)	1309 (18.05%)	6780 (18.89%)	420 (13.57%)	7580 (19.18%)	90 (16.98%)	62 297 (17.54%)
3	6846 (15.87%)	1135 (15.65%)	5711 (15.91%)	251 (8.11%)	6501 (16.45%)	94 (17.74%)	40 283 (11.34%)
4	5261 (12.19%)	921 (12.70%)	4340 (12.09%)	157 (5.07%)	5061 (12.80%)	43 (8.11%)	22 694 (6.39%)
≥5	11 506 (26.67%)	2104 (29.02%)	9401 (26.19%)	233 (7.53%)	11 158 (28.23%)	115 (21.70%)	29 665 (8.35%)
Proton pump inhibitor use							
Yes	30 841 (71.47%)	5400 (74.47%)	25 440 (70.87%)	1860 (60.12%)	28 582 (72.31%)	399 (75.28%)	162 218 (45.67%)
No	12 309 (28.53%)	1851 (25.53%)	10 457 (29.13%)	1234 (39.88%)	10 944 (27.69%)	131 (24.72%)	192 954 (54.33%)
H_2 receptor antagonists							
Yes	3175 (7.36%)	629 (8.67%)	2546 (7.09%)	275 (8.89%)	2855 (7.22%)	45 (8.49%)	16 182 (4.56%)
No	39 975 (92.64%)	6622 (91.33%)	33 351 (92.91%)	2819 (91.11%)	36 671 (92.78%)	485 (91.51%)	338 990 (95.54%)
Antibiotics							
Yes	41 893 (97.09%)	7145 (98.54%)	34 746 (96.79%)	3072 (99.29%)	38 291 (96.88%)	530 (100.00%)	304 851 (85.83%)
No	1257 (2.91%)	106 (1.46%)	1151 (3.21%)	22 (0.71%)	1235 (3.12%)	0 (0.00%)	50 321 (14.17%)
NSAIDs							
Yes	25 441 (58.96%)	4487 (61.88%)	20 953 (58.37%)	2096 (67.74%)	16 530 (41.82%)	349 (65.85%)	209 911 (59.10%)
No	17 709 (41.04%)	2764 (38.12%)	14 944 (41.63%)	998 (32.26%)	22 996 (58.18%)	181 (34.15%)	145 261 (40.90%)
Aspirin							
Yes	22 051 (51.10%)	3851 (53.11%)	17 698 (49.30%)	766 (24.76%)	21 057 (53.27%)	228 (43.02%)	136 404 (38.41%)
No	21 099 (48.90%)	3400 (46.89%)	18 199 (50.70%)	2328 (75.24%)	18 469 (46.73%)	302 (56.98%)	218 768 (61.59%)
Other prescribed drugs							
Yes	43 064 (99.80%)	7248 (99.96%)	35 814 (99.77%)	3086 (99.74%)	39 448 (99.80%)	530 (100.00%)	355 172 (100.00%)
No	86 (0.20%)	3 (0.04%)	83 (0.23%)	8 (0.26%)	78 (0.20%)	0 (0.00%)	0 (0.00%)

CDI, *Clostridioides difficile* infection; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; SD.
[a] For the controls, age and year at time of the first CDI date of their matched case was used.
[b] Controls with a history of CDI were excluded from this study.

6.3–6.4) (Table 2). Compared with the matched controls, these mortality rates were quite similar across age groups (<65 years IRR = 11.5, 95% CI: 10.6–12.5; ≥65 years IRR = 13.8, 95% CI: 13.5–14.2) (Table 3). These mortality rates were higher than the non-stratified mortality rate, as the interaction term between CDI and age was omitted due to collinearity. Furthermore, men had higher mortality rates (SMR = 7.6, 95% CI: 7.4–7.7; IRR = 4.2, 95% CI: 3.0–4.5) than women (SMR = 6.2, 95% CI: 6.1–6.3; IRR = 2.8, 95% CI: 2.7–3.0) (Tables 2 and 3).

Comorbidities

Compared with the matched controls, individuals with CDI had the highest mortality rates among those without comorbidities (IRR = 6.1, 95% CI: 5.5–6.8) and those with the highest comorbidity scores (IRR = 3.3, 95% CI: 2.8–3.8) (Table 3). No statistically significant association was found between CDI and mortality for those with comorbidity scores 3–4.

Hospital-versus community-acquired CDI

Among individuals with hospital-acquired CDI, 30.5% (N = 2632) of the <65-year-old group and 75.5% (N = 23 330) of the ≥65-year-old group died, compared with a respective 4.2% (N = 86) and 35.0% (N = 369) among the community-acquired group.

Hospital-acquired CDI was associated with higher mortality rates than community-acquired CDI (IRR = 2.4, 95% CI: 1.9–3.2), especially among the older age group (≥65 IRR = 12.6, 95% CI:

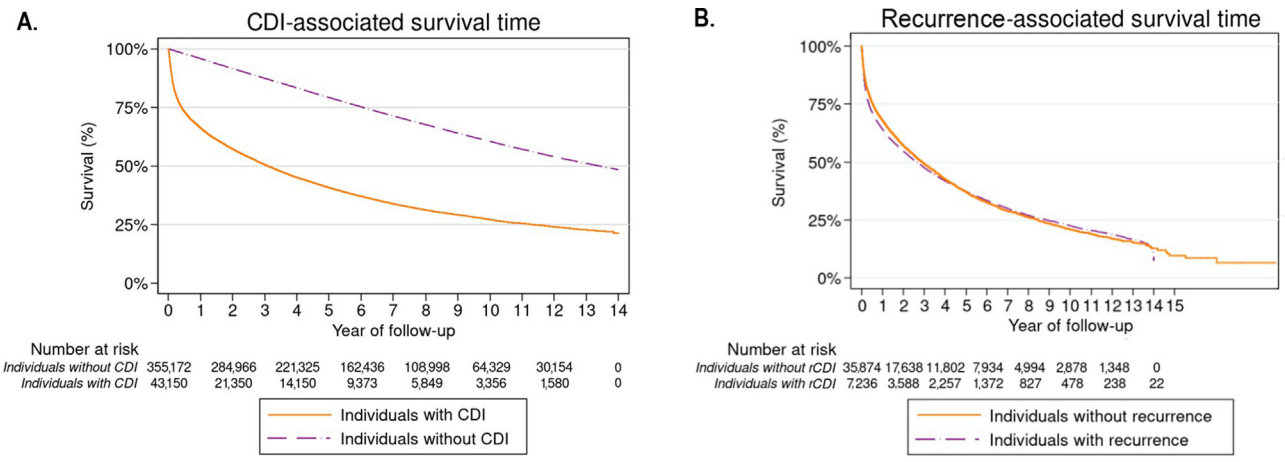

Fig. 1. Survival time of individuals (a) with and without *Clostridioides difficile* infection (CDI), from first CDI diagnosis of the (corresponding) case onwards, and (b) with and without recurrent CDI (rCDI), from first recurrence onwards.

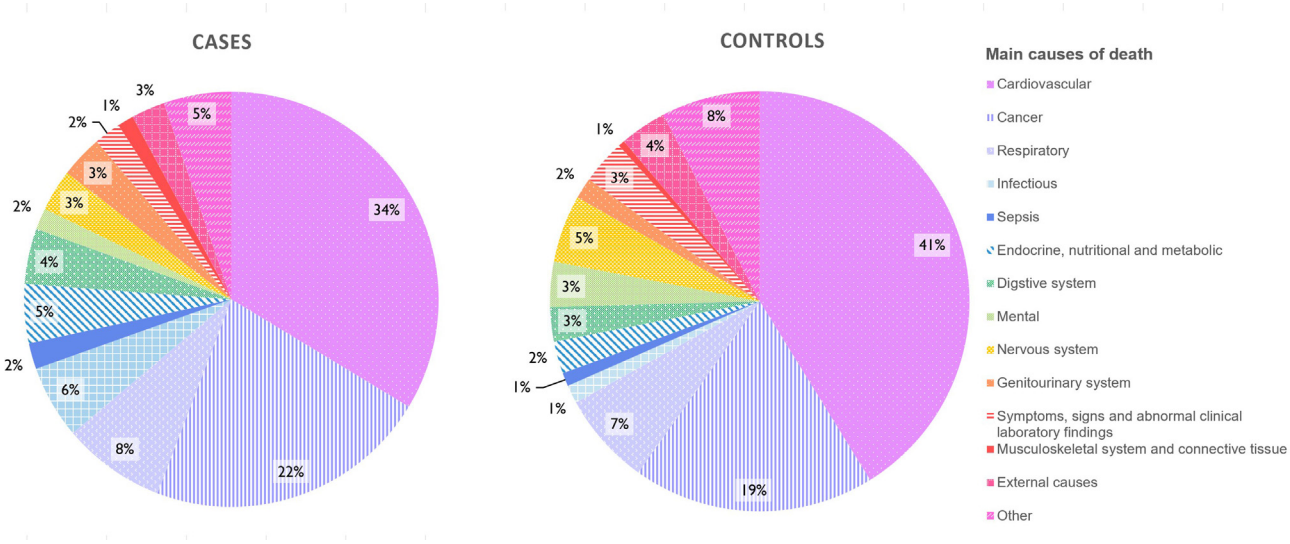

Fig. 2. Main causes of death among individuals with and without *Clostridioides difficile* infection (CDI).

Table 2
Overall risk of dying following at least one CDI episode, expressed as standardized mortality ratios (SMRs) and 95% CIs, stratified by age, sex, and cause of death. Swedish population

	SMR (95% CI)			*P* for trend[a]	*P* for inter-action[b]
	All ages	0–64 y	≥65 y		
All-cause					
Total	6.77 (6.69–6.86)	27.35 (26.24–28.50)	6.33 (6.25–6.41)	<0.001	<0.001
Male	7.56 (7.43–7.70)	27.52 (25.98–29.13)	7.03 (6.91–7.16)	<0.001	<0.001
Female	6.18 (6.08–6.29)	27.16 (25.56–28.84)	5.81 (5.71–5.91)	<0.001	<0.001
Cardiovascular					
Total	11.30 (11.13–11.47)	53.46 (49.90–57.21)	10.86 (10.69–11.03)	<0.001	<0.001
Male	12.69 (12.42–12.97)	47.90 (43.7–52.35)	12.12 (11.85–12.40)	<0.001	<0.001
Female	10.28 (10.07–10.50)	63.72 (57.23–70.75)	9.94 (9.73–10.15)	<0.001	<0.001
Cancer					
Total	8.75 (8.55–8.95)	36.06 (33.92–39.30)	7.75 (7.56–7.95)	<0.001	<0.001
Male	9.57 (9.27–9.87)	45.85 (41.99–49.99)	8.54 (8.25–8.83)	<0.001	<0.001
Female	7.96 (7.69–8.23)	29.91 (27.43–32.55)	6.99 (6.74–7.26)	<0.001	<0.001

CDI, *Clostridioides difficile* infection.
[a] Age was modelled categorically to assess linear trend over age categories.
[b] Interaction between CDI and age was assessed.

Table 3
Mortality risk after at least one CDI episode, expressed as adjusted incidence rate ratios (IRRs) and 95% CIs, comparing individuals with CDI with their matched individuals without CDI, comparing individuals with recurrent (rCDI) with individuals with non-recurrent (non-rCDI) CDI, and individuals with community-with individuals with hospital-acquired CDI

Strata	Total cases (43 150) vs. controls (355 172)		rCDI (n = 7251) vs. non-rCDI (n = 35 897)		Hospital- (n = 39 526) vs. community-acquired (n = 3094)	
	Number of deaths among CDI cases (%)	Adjusted incidence rate ratio (95% CI)[a]	Number of deaths among rCDI cases (%)	Adjusted incidence rate ratio (95% CI)[b]	Number of deaths among hospital-acquired cases (%)	Adjusted incidence rate ratio (95% CI)[c]
All	26 597 (61.64%)	3.47 (3.32–3.63)	4236 (58.42%)	0.24 (0.22–0.26)	25 962 (65.68%)	2.43 (1.85–3.20)
Sex						
Male	12 709 (64.25%)	4.20 (3.04–4.46)	1968 (62.58%)	0.43 (0.38–0.48)	12 408 (67.67%)	2.76 (1.82–4.18)
Female	13 888 (59.43%)	2.84 (2.66–3.04)	2268 (55.24%)	0.14 (0.13–0.16)	13 554 (63.96%)	1.77 (1.22–2.56)
Age groups						
0–64	2748 (25.25%)	11.51 (10.62–12.49)	423 (24.87%)	0.45 (0.37–0.54)	2632 (30.52%)	7.30 (5.38–9.89)
≥65	23 849 (73.91%)	13.83 (13.48–14.19)	3813 (68.70%)	1.23 (1.14–1.32)	23 330 (75.506%)	12.56 (10.15–15.56)
Charlson Comorbidity score						
0	1329 (21.69%)	6.11 (5.47–6.84)	171 (18.04%)	0.06 (0.05–0.08)	1288 (28.38%)	0.50 (0.25–0.99)
1	2809 (52.79%)	1.45 (1.29–1.63)	392 (47.00%)	0.06 (0.04–0.07)	2737 (58.40%)	0.16 (0.09–0.28)
2	5105 (63.10 %)	1.91 (1.76–2.07)	754 (57.60%)	0.22 (0.18–0.26)	4981 (65.71%)	1.88 (1.23–2.86)
3	4697 (68.61%)	0.88 (0.80–0.98)	740 (65.20%)	0.03 (0.02–0.03)	4571 (70.31%)	0.18 (0.11–0.30)
4	3799 (72.21%)	0.92 (0.81–1.05)	628 (68.19%)	0.08 (0.06–0.09)	3712 (73.35%)	0.06 (0.03–0.11)
≥5	8858 (76.99%)	3.32 (2.87–3.83)	1551 (73.72%)	0.00 (0.00–0.00)	8673 (77.73%)	1335.97 (408.62–4367.90)
Drug ever-use						
Antibiotics	25 552 (60.99%)	2.26 (2.15–2.37)	4154 (58.14%)	0.21 (0.19–0.23)	24 921 (65.08%)	2.35 (1.78–3.10)
PPIs	19 206 (62.27%)	2.08 (1.96–2.21)	3211 (59.46%)	0.17 (0.15–0.19)	18 735 (65.55%)	3.36 (2.41–4.68)
H_2Rs	1745 (54.96%)	1.44 (1.19–1.76)	319 (50.72%)	0.18 (0.12–0.25)	1682 (58.91 %)	0.64 (0.32–1.29)
NSAIDs	14 001 (55.03%)	1.82 (1.72–1.94)	2341 (52.17%)	0.24 (0.22–0.28)	13 625 (59.25%)	2.40 (1.76–3.27)
Aspirin	16 029 (72.69%)	1.42 (1.32–1.53)	2626 (68.19%)	0.36 (0.31–0.419)	15 678 (74.46%)	2.65 (1.50–4.71)

Matched population.
CCI, Charlson Comorbidity Index; CDI, *Clostridioides difficile* infection; H_2R, H_2-receptor antagonist; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.
[a] Comparing cases with controls, and adjusted for sex, age (as a continuous variable), CCI, drug ever-use, the interaction (term) between CDI and CCI (as a continuous variable), and the interaction between CDI and age categories (as 0–64 and ≥ 65 y). Age and CCI scores were modelled as continuous variables to prevent information loss. In all models, the interaction between age group ≥65 and CDI, recurrent CDI, or hospital-acquired CDI was omitted because of collinearity.
[b] Comparing rCDI cases with non-rCDI cases, and adjusted for sex, age (as continuous variable), CCI (as a continuous variable), drug ever-use, community- and hospital-acquired CDI, the interaction (term) between recurrence and CCI, and the interaction between recurrence and age categories (categorized as 0–64 and 65+ y). Age and CCI scores were modelled as continuous variables to prevent information loss. Recurrent cases (and their matched controls) were followed from their first recurrent episode, others from the first CDI episode. In all models, the interaction between age group ≥65 and CDI, recurrent CDI, or hospital-acquired CDI was omitted because of collinearity.
[c] Comparing hospital-acquired cases with community-acquired cases, and adjusted for sex, age (as continuous variable), CCI, and drug ever-use. Age and CCI scores were modelled as continuous variables to prevent information loss. In all models, the interaction between age group ≥65 and CDI, recurrent CDI, or hospital-acquired CDI was omitted because of collinearity.

10.2–15.6; <65 IRR = 7.3, 95% CI: 5.4–9.9) (Table 3). There were no differences between men and women (IRR = 2.8, 95% CI: 1.8–4.2; and IRR = 1.8, 95% CI: 1.2–2.6, respectively).

The most significant increase in mortality rates was found among the highest comorbidity scores (IRR = 1336.0, 95% CI: 408.6–4367.9). Among lower comorbidity scores, community-acquired CDI was associated with higher mortality rates than hospital-acquired CDI (score 0 IRR = 0.5, 95% CI: 0.2–1.0; score 1 IRR = 0.16, 95% CI: 0.1–0.3; score 3 IRR = 0.2, 95% CI: 0.1–0.3; score 4 IRR = 0.1, 95% CI: 0.0–0.01) (Table 3).

Recurrent versus non-recurrent CDI

Among individuals with rCDI, 24.9% (N = 423) of the <65-year-old group and 68.7% (N = 3813) of the 65-year-old group died, compared with a respective 25.3% (N = 2325) and 75.0% (N = 20 036) among individuals with non-rCDI (data not shown).

Recurrence was associated with lower mortality rates than non-recurrence (IRR = 0.2, 95% CI: 0.2–0.3) (Table 3). Lower mortality rates were additionally found among the younger individuals, among sexes, all comorbidity groups, and all prescribed drug groups. Among the elderly, mortality rates were slightly higher among individuals without rCDI than those with rCDI (IRR = 1.2, 95% CI: 1.1–1.3).

Discussion

This study is one of the largest population-based cohorts following individuals with CDI up to 14 years, presenting an in-depth evaluation of CDI-related mortality. Our findings indicate that individuals with CDI had a 3- to 7-fold higher mortality compared with the Swedish background population and their matched controls. Most individuals with CDI died early (within 30 days) from cardiovascular- or cancer-related causes, although the mortality risk remained increased even 1 year after diagnosis. These mortality rates were higher among individuals with hospital-acquired than community-acquired CDI. The risk of death was also higher for first infections than for recurrent infections. In other words, if people die from CDI, it seems they die in the hospital because of the first episode, not the recurrence(s). Survival bias and underlying comorbidities may play a role, and although we adjusted for chronic comorbidities, residual confounding by comorbidities and frailty is likely. Mortality risks were, however, still significantly increased when we restricted our analyses to those without comorbidities.

Previous research, focusing on hospitalized patients, attributed the increased mortality mainly to comorbidities [16,18,22]. These studies had much shorter follow-ups [16,18] or included smaller samples than our study [22]. Furthermore, this study included individuals with community-acquired CDI (8.4% of all included cases), who were generally younger and healthier than individuals with hospital-acquired CDI. Those with community-acquired CDI were probably less healthy than their peers and might have had more contact with healthcare (e.g. dialysis, day surgery, and healthcare workers), which needs further exploration. Nevertheless, residual confounding by poorer temporary or chronic overall health among hospital- and community-acquired cases cannot be out-ruled. Higher frailty may also explain the higher mortality among those

without a recurrence than those with a recurrence, a finding also described in large cohort studies from the United States and Japan [19,23,24], yet contradicted by other studies [25,26]. This distinction could have occurred because we investigated individuals of every age in both in- and outpatient care (leading to high coverage, including the less severe CDI episodes), whereas previous studies were restricted to only elderly [26] or only adults in inpatient care [25]. Our results also indicated a slightly higher mortality among elderly individuals with rCDI compared with elderly individuals without rCDI, which is more similar to previous research [25,26].

Other studies have shown that CDI strains can present with different antimicrobial susceptibility patterns, severity of clinical presentation, risk of recurrence, and even mortality [27–30]. A recent study indicated important differences between ribotypes in community-acquired and hospital-acquired CDI [31]. The hypervirulent ribotype RT027 has been linked to only a few sporadic outbreaks in Sweden and seems relatively rare in Sweden compared with other European countries [31,32]. However, strain information is not available in the Swedish nationwide Patient Registry, and could therefore neither be assessed in our present study, nor in a recent large European study addressing CDI mortality [22].

Previously described hazard ratios around 1.5 and 2.5 [10,14,17] are lower than our incidence rate ratio of 3.5, possibly because of different statistical methods and study populations (e.g. only inpatients over 18 years old) [10,14,17]. Moreover, previous work has established that older age increases the mortality risk among CDI patients [19,22], whereas our SMR results indicate an increased mortality risk for younger people after exposure to CDI (particularly when compared with the background population). Nevertheless, younger individuals had an overall lower absolute probability of death compared with the elderly. Our younger patients with CDI mostly die from cardiology or oncological causes and are likely seriously ill.

An important strength is our population-based design including all recorded CDI cases in Sweden during our study period, while comparing them with the Swedish population, hence increasing the statistical power and generalizability of the results. The matched-cohort design facilitated adjustment for several potential confounders including comorbidities and prescription drug use. The validity was high because of the overall complete, high-quality registries. The Patient Registry captures 85–95% of all inpatient care diagnoses, and 80% of all hospital-based outpatient health care, although CDI has not been validated to our knowledge [33]. The Swedish Prescribed Drug Registry has <0.3% missing patient identification data and includes 45–100% of the entire population annually, or 85% between 2005 and 2014 (depending on age group, i.e. proportion using prescribed drugs each year) [34,35]. The Causes of Death Registry is complete for all deaths among the Swedish residents from 1991 onwards and captures approximately 98–99% of all causes of death [36]. Finally, the study design was conducted based on an *a priori* written study protocol.

As CDI reporting is not mandatory in Sweden, and CDI may remain undiagnosed, particularly milder cases may be missed. This misclassification occurred in at least 84 controls (0.02%) with CDI as main or underlying cause of death among controls. Nevertheless, the Swedish CDI reporting is probably more complete than in most countries, as suggested by the relatively high incidence [6]. Community-acquired CDI could additionally be underrepresented in this study, because we lacked information whether individuals were diagnosed with CDI within 3 days after in-hospital admission, classifying those as having hospital-acquired CDI. Unfortunately, because of the registry nature of the data, no clinical data on CDI severity, applied diagnostic tests or clinical practices regarding CDI diagnosis, or clinical parameters are available. Furthermore, misclassification could have occurred for drug exposure, because inpatient- and over-the-counter drug use was not included in the Drug Registry. PPIs, NSAIDs, and aspirin can be sold without prescription, but in smaller packages at higher prices.

Confounding by underlying pathophysiology could have occurred during this study because comorbidities are associated with CDI and higher mortality—making it difficult to distinguish if CDI is a main or contributing cause, and if it actually affected survival duration. Results of the matched cohort were, however, adjusted for comorbidities.

Because this project is part of a larger CDI project, matching may not have been ideal for this sub-study. Yet, even after exclusions, we do include more controls than generally recommended (up to ten) even if some of the originally selected controls turned out to be ineligible. A sensitivity analysis including only optimally (1:10) matched cases and controls (who were alive at the time of the first recorded CDI episode) showed similar results. It seems likely that CDI is an important cause of mortality, especially within the first 30 days. Although CDI is a known serious infection for older patients with several comorbidities, this study found a non-negligible impact on younger patients and both patients with and without comorbidities. Furthermore, it seems that people are most likely to die after the first CDI episode, and less likely after recurrence(s). People with hospital-acquired CDI were also more likely to die than those with community-acquired CDI, with death among the community-acquired group being rare.

To conclude, CDI was associated with elevated all-cause and cause-specific mortality, in both sexes, all age groups, comorbidity groups, and among individuals with hospital-acquired CDI, with mortality being highest during a first episode of CDI.

Author contributions

A.B., F.L.A., L.E., E.V., S.C., J.S., and N.B. were involved in the study concept and design. A.B. conducted the statistical analyses under the supervision of J.S. and N.B. All authors interpreted the findings. A.B. drafted the manuscript together with J.S. and N.B., which all other authors critically revised. All authors approve the current version for submission. N.B. is the guarantor of the study.

Transparency declaration

Conflict of interest

The authors declare no conflict of interest. At the time of the study, F.L.A. was employed by Ferring Pharmaceuticals, which conducts research into the microbiome area.

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Data availability

The dataset from this study is held securely in coded form at Karolinska Institutet, yet it belongs to the National Board of Health and Welfare. Data-sharing agreements prohibit making the dataset publicly available. However, the data can be made available upon reasonable request to the corresponding author (NB) after obtaining the necessary ethical and data-sharing approvals. The underlying analysis plan is available from the corresponding author (NB) upon request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2023.07.008.

References

[1] Khanna S, Pardi DS. The growing incidence and severity of *Clostridium difficile* infection in inpatient and outpatient settings. Exp Rev Gastroenterol Hepatol 2010;4:409–16. https://doi.org/10.1586/egh.10.48.
[2] Cawcutt KA, Zimmer A. Chapter 95 – management of infection in patients with kidney transplant. In: Ronco C, Bellomo R, Kellum JA, Ricci Z, editors. Critical care nephrology. 3rd ed. Philadelphia: Elsevier; 2019. 552–560.e1.
[3] Verstraeten T, Cattaert T, Harris J, Lopman B, Tam CC, Ferreira G. Estimating the burden of medically attended norovirus gastroenteritis: modeling linked primary care and hospitalization datasets. J Infect Dis 2017;216:957–65. https://doi.org/10.1093/infdis/jix410.
[4] Schmid D, Kuo HW, Simons E, Kanitz EE, Wenisch J, Allerberger F, et al. All-cause mortality in hospitalized patients with infectious diarrhea: *Clostridium difficile* versus other enteric pathogens in Austria from 2008 to 2010. J Infect Public Health 2014;7:133–44. https://doi.org/10.1016/j.jiph.2013.07.010.
[5] Magill SS, O'Leary E, Janelle SJ, Thompson DL, Dumyati G, Nadle J, et al. Changes in prevalence of health care–associated infections in US hospitals. N Engl J Med 2018;379:1732–44. https://doi.org/10.1056/NEJMoa1801550.
[6] Balsells E, Shi T, Leese C, Lyell I, Burrows J, Wiuff C, et al. Global burden of *Clostridium difficile* infections: a systematic review and meta-analysis. J Glob Health 2019;9:010407. https://doi.org/10.7189/jogh.09.010407.
[7] Eze P, Balsells E, Kyaw MH, Nair H. Risk factors for *Clostridium difficile* infections – an overview of the evidence base and challenges in data synthesis. J Glob Health 2017;7:010417. https://doi.org/10.7189/jogh.07.010417.
[8] Ananthakrishnan AN. *Clostridium difficile* infection: epidemiology, risk factors and management. Nat Rev Gastroenterol Hepatol 2011;8:17–26. https://doi.org/10.1038/nrgastro.2010.190.
[9] Masgala A, Delis SG, Dervenis C. *Clostridium difficile* infection: an increasing postsurgical complication. J Infect Dis Ther 2014;2:176. https://doi.org/10.4172/2332-0877.1000176.
[10] Enoch DA, Murray-Thomas T, Adomakoh N, Dedman D, Georgopali A, Francis NA, et al. Risk of complications and mortality following recurrent and non-recurrent *Clostridioides difficile* infection: a retrospective observational database study in England. J Hosp Infect 2020;106:793–803. https://doi.org/10.1016/j.jhin.2020.09.025.
[11] Fu Y, Luo Y, Grinspan AM. Epidemiology of community-acquired and recurrent *Clostridioides difficile* infection. Therap Adv Gastroenterol 2021;14:17562848211016248. https://doi.org/10.1177/17562848211016248.
[12] Zilberberg MD, Reske K, Olsen M, Yan Y, Dubberke ER. Risk factors for recurrent *Clostridium difficile* infection (CDI) hospitalization among hospitalized patients with an initial CDI episode: a retrospective cohort study. BMC Infect Dis 2014;14:306. https://doi.org/10.1186/1471-2334-14-306.
[13] Zilberberg MD, Shorr AF, Wang L, Baser O, Yu H. Development and validation of a risk score for *Clostridium difficile* infection in Medicare beneficiaries: a population-based cohort study. J Am Geriatr Soc 2016;64:1690–5. https://doi.org/10.1111/jgs.14236.
[14] Olsen MA, Stwalley D, Demont C, Dubberke ER. *Clostridium difficile* infection increases acute and chronic morbidity and mortality. Infect Control Hosp Epidemiol 2019;40:65–71. https://doi.org/10.1017/ice.2018.280.
[15] Nanwa N, Sander B, Krahn M, Daneman N, Lu H, Austin PC, et al. A population-based matched cohort study examining the mortality and costs of patients with community-onset *Clostridium difficile* infection identified using emergency department visits and hospital admissions. PLOS ONE 2017;12:e0172410. https://doi.org/10.1371/journal.pone.0172410.
[16] Banks A, Moore EK, Bishop J, Coia JE, Brown D, Mather H, et al. Trends in mortality following *Clostridium difficile* infection in Scotland, 2010–2016: a retrospective cohort and case–control study. J Hosp Infect 2018;100:133–41. https://doi.org/10.1016/j.jhin.2018.07.023.
[17] Hensgens MPM, Goorhuis A, Dekkers OM, van Benthem BHB, Kuijper EJ. All-cause and disease-specific mortality in hospitalized patients with *Clostridium difficile* infection: a multicenter cohort study. Clin Infect Dis 2013;56:1108–16. https://doi.org/10.1093/cid/cis1209.
[18] Chintanaboina J, Navabi S, Suchniak-Mussari K, Stern B, Bedi S, Lehman EB, et al. Predictors of 30-day mortality in hospitalized patients with *Clostridium difficile* infection. South Med J 2017;110:546–9. https://doi.org/10.14423/smj.0000000000000687.
[19] Appaneal HJ, Caffrey AR, Beganovic M, Avramovic S, LaPlante KL. Predictors of mortality among a national cohort of veterans with recurrent *Clostridium difficile* infection. Open Forum Infect Dis 2018;5:ofy175. https://doi.org/10.1093/ofid/ofy175.
[20] Song JH, Kim YS. Recurrent *Clostridium difficile* infection: risk factors, treatment, and prevention. Gut Liver 2019;13:16–24. https://doi.org/10.5009/gnl18071.
[21] National Board of Health and Welfare (Socialstyrelsen). Statistics on Causes of Death. Report 2021-6-7453. https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/statistik/2021-6-7454.pdf
[22] Czepiel J, Krutova M, Mizrahi A, Khanafer N, Enoch DA, Patyi M, et al. Mortality following *Clostridioides difficile* infection in Europe: a retrospective multicenter case-control study. Antibiotics (Basel) 2021;10:299. https://doi.org/10.3390/antibiotics10030299.
[23] Reveles KR, Lawson KA, Mortensen EM, Pugh MJV, Koeller JM, Argamany JR, et al. National epidemiology of initial and recurrent *Clostridium difficile* infection in the Veterans Health Administration from 2003 to 2014. PLOS ONE 2017;12:e0189227. https://doi.org/10.1371/journal.pone.0189227.
[24] Kimura T, Stanhope S, Sugitani T. Excess length of hospital stay, mortality and cost attributable to *Clostridioides (Clostridium) difficile* infection and recurrence: a nationwide analysis in Japan. Epidemiol Infect 2020;148:e65. https://doi.org/10.1017/s0950268820000606.
[25] Olsen MA, Yan Y, Reske KA, Zilberberg MD, Dubberke ER. Recurrent *Clostridium difficile* infection is associated with increased mortality. Clin Microbiol Infect 2015;21:164–70. https://doi.org/10.1016/j.cmi.2014.08.017.
[26] Feuerstadt P, Nelson WW, Drozd EM, Dreyfus J, Dahdal DN, Wong AC, et al. Mortality, health care use, and costs of *Clostridioides difficile* infections in older adults. J Am Med Dir Assoc 2022;23:1721. https://doi.org/10.1016/j.jamda.2022.01.075. 8.e19.
[27] Carlson TJ, Blasingame D, Gonzales-Luna AJ, Alnezary F, Garey KW. *Clostridioides difficile* ribotype 106: a systematic review of the antimicrobial susceptibility, genetics, and clinical outcomes of this common worldwide strain. Anaerobe 2020;62:102142. https://doi.org/10.1016/j.anaerobe.2019.102142.
[28] Herbert R, Hatcher J, Jauneikaite E, Gharbi M, d'Arc S, Obaray N, et al. Two-year analysis of *Clostridium difficile* ribotypes associated with increased severity. J Hosp Infect 2019;103:388–94. https://doi.org/10.1016/j.jhin.2019.06.003.
[29] Magnusson C, Wullt M, Löfgren S, Iveroth P, Akerlund T, Matussek A. Ribotyping of *Clostridium difficile* strains associated with nosocomial transmission and relapses in a Swedish County. APMIS 2013;121:153–7. https://doi.org/10.1111/j.1600-0463.2012.02950.x.
[30] van Rossen TM, Ooijevaar RE, Vandenbroucke-Grauls C, Dekkers OM, Kuijper EJ, Keller JJ, et al. Prognostic factors for severe and recurrent *Clostridioides difficile* infection: a systematic review. Clin Microbiol Infect 2022;28:321–31. https://doi.org/10.1016/j.cmi.2021.09.026.
[31] Enkirch T, Mernelius S, Magnusson C, Kühlmann-Berenzon S, Bengnér M, Åkerlund T, et al. Molecular epidemiology of community- and hospital-associated *Clostridioides difficile* infections in Jönköping, Sweden, October 2017-March 2018. APMIS 2022;130:661–70. https://doi.org/10.1111/apm.13270.
[32] Freeman J, Vernon J, Pilling S, Morris K, Nicolson S, Shearman S, et al. Five-year Pan-European, longitudinal surveillance of *Clostridium difficile* ribotype prevalence and antimicrobial resistance: the extended ClosER study. Eur J Clin Microbiol Infect Dis 2020;39:169–77. https://doi.org/10.1007/s10096-019-03708-7.
[33] Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;11:450. https://doi.org/10.1186/1471-2458-11-450.
[34] Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, et al. The new Swedish Prescribed Drug Register–opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf 2007;16:726–35. https://doi.org/10.1002/pds.1294.
[35] Brusselaers N, Lagergren J. Maintenance use of non-steroidal anti-inflammatory drugs and risk of gastrointestinal cancer in a nationwide population-based cohort study in Sweden. BMJ Open 2018;8:e021869. https://doi.org/10.1136/bmjopen-2018-021869.
[36] Brooke HL, Talbäck M, Hörnblad J, Johansson LA, Ludvigsson JF, Druid H, et al. The Swedish cause of death register. Eur J Epidemiol 2017;32:765–73. https://doi.org/10.1007/s10654-017-0316-1.